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Celecoxib versus placebo as an adjunct to treatment-as-usual in children and youth with obsessive-compulsive disorder: Protocol for a single-site randomized quadruple-blind phase II study

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Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ASD, autism spectrum disorder; BMI, body mass index, BCCH, British Columbia Children's Hospital; CGI, clinical global impression; CNS, central nervous system; C&W, Children's and Women's Health Centre; CBC, complete blood count; Cr, creatinine, COX, cyclooxygenase; CY-BOCS, Children's Yale-Brown Obsessive Compulsive Scale (Version I); CY-BOCS II, Children's Yale-Brown Obsessive Compulsive Scale (Version II); DSMB, data safety monitoring board; eCRF, electronic case report form; MDD, major depressive disorder; MINI-Kid, Mini International Neuropsychiatric Interview for Children and Adolescents; NSAID, Non-steroidal anti-inflammatory drug; OCD, obsessive-compulsive disorder; OCI-CV, Obsessive Compulsive Inventory – Child Version; PANS, pediatric acute neuropsychiatric syndrome; PANDAS, pediatric autoimmune disorder associated with streptococcal infections; PGI, patient global impression; PPQ, Participant Perspective Questionnaire; RCT, randomized controlled trial; RA, Research Assistant; REDCap, Research Electronic Data Capture; REB, Research Ethics Board; SMURF, Safety Monitoring Uniform Research Form; SRI, serotonin reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor

ABSTRACT

Background: Cyclooxygenase (COX) enzymes oxidize arachidonic acid to prostaglandins, which modulate neuronal function and inflammation in the central nervous system. Consensus guidelines recommend NSAIDs as an adjunctive approach in adults with obsessive-compulsive disorder (OCD) and in children with acute-onset OCD subtypes. However, there is limited evidence to support this approach. The primary objective of this study is to determine the efficacy of the COX-2-selective inhibitor celecoxib as an adjunct to treatment-as-usual in children and youth with moderate-to-severe OCD.

Methods: The Adjunctive CElecoxib in childhood-onset OCD (ACE-OCD) study is a single-centre randomized, quadruple-blind, placebo-controlled superiority trial with two parallel groups: celecoxib 100 mg twice daily and placebo. Target recruitment is 80 participants ages 7-18 with no recent treatment changes. The primary outcome is OCD severity after 12 weeks of treatment, measured by clinician-administered Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS). Secondary outcomes include CY-BOCS score after 6 weeks; difference in the proportion of participants achieving a clinically meaningful response or remission; mean clinical global impression of severity and improvement after 6 and 12 weeks; and proportion of participants reporting adverse events possibly or probably related to the study intervention. The primary analyses, carried out according to intention-to-treat principles, will compare the celecoxib to placebo group on each outcome of interest, adjusting for baseline scores using analysis of covariance or logistic regression. Participants will be offered a 12-week open-label celecoxib extension and will be invited to participate in an ancillary study for biomarker analyses.

Ethics and dissemination: This protocol has been approved by the University of British Columbia Children's and Women's Research Ethics Board and has received a No Objection Letter from Health Canada. The findings will be disseminated in peer-reviewed journals and presentations to multiple stakeholders including patients, parents, and health care providers.

Trial registration number: NCT04673578. Open for recruitment.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study is the first randomized, placebo-controlled trial to evaluate the efficacy and safety of adjunctive NSAID therapy in childhood-onset OCD and does not restrict participants to a diagnosis of pediatric acute-onset neuropsychiatric syndrome (PANS) or pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS).
- Study visits may occur virtually and screening blood work can be completed in participants' local communities, increasing accessibility for participants.
- Participants will have the option to consent to an ancillary study involving biosample collection for correlative biology; this will provide preliminary longitudinal data allowing measurement of associations between inflammatory biomarkers and clinical phenotype.
- This study incorporates assessment of participants' and parents' perspectives on participation, including their experience of virtual visits, to inform future studies of psychopharmacologic interventions in this population.
- While heterogeneity of usual therapy may limit power to detect differences between arms, this represents a more pragmatic approach than contemporaneous initiation of a selective serotonin reuptake inhibitor as described in preliminary studies in adults.

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a common neuropsychiatric condition identified by the World Health Organization as one of the leading causes of worldwide medical disability[1]. It affects 1-3% of the population and places significant burden on patients, families, and healthcare systems[2]. Childhood-onset OCD (CO-OCD) represents a specific subtype with unique epidemiological, etiological, and clinical characteristics[3,4]. Although cognitive behavioural therapy (CBT) and serotonin reuptake inhibitors (SRIs) are effective treatments, there is a critical need to develop novel and augmenting agents for patients with enduring symptoms.

A large body of work suggests an association between infection and an abrupt, early-onset form of OCD, termed pediatric autoimmune disorder associated with streptococcal infections (PANDAS)[5], as well as pediatric acute neuropsychiatric syndrome (PANS)[6]. Recent epidemiological data suggest that recurrent episodes of infection and inflammation are associated with the development of multiple mental disorders in children[7], including "classic" OCD[8]. Moreover, patients with autoimmune disorders have higher rates of comorbid OCD compared to the general population[9,10]. A recent cohort study based on Swedish National Register data suggested increased rates of multiple autoimmune diseases among patients with OCD and their first-degree relatives[11]; we have also described higher-than-expected rates of immune-related conditions in individuals with CO-OCD[12]. Positron emission tomography imaging study in adults with OCD has demonstrated increased volume of translocator protein-18 distribution in cortico-striato-thalamo-cortical circuits, implicating widespread microglial activation[13]. It is unclear whether changes in cellular and soluble inflammatory markers represent underlying etiology, a consequence of disease progression, or associated epiphenomena.

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase (COX) enzymes, which catalyze the metabolism of arachidonic acids to prostanoids. COX-2 and its products play an important physiological role in synaptic plasticity and long-term potentiation and may also contribute to neuropathology by enhancing glutamate excitotoxicity, promoting neuronal cell death, and oxidizing endogenous cannabinoids[14,15]. Recent meta-analyses suggest a potential role of adjunctive COX-2 inhibitors in the treatment of depression[16] and first-episode schizophrenia[17,18]. Behavioral effects of COX inhibition may relate not only to anti-inflammatory activity but also to direct effects on neuronal function and synaptic transmission. Consensus guidelines on the use of anti-inflammatory therapy in children with PANDAS suggest NSAIDs as first-line options for patients with mild impairment[19]. However, a recent systematic review of treatment for PANS/PANDAS found insufficient evidence to support this practice[20]. In adults with OCD, two small randomized-controlled trials have suggested modest symptom improvement with celecoxib as an adjunct to fluoxetine or fluvoxamine[21,22]. This raises the possibility that COX-2 inhibition may be effective in a general OCD population[23]. However, no controlled studies to date have tested the effects of COX inhibitors in CO-OCD. The present study will determine the efficacy of the COX-2-selective inhibitor celecoxib as an adjunct to treatment-as-usual in children and youth with moderate-to-severe OCD.

METHODS AND DESIGN

Study design

The ACE-OCD trial is a randomised, quadruple-blinded, placebo-controlled, single-site study comparing a 12-week course of twice daily celecoxib with placebo as an adjunct to treatment-as-usual in children and youth with moderate-to-severe OCD between the ages of 7 and 18. The protocol was drafted in accordance with the SPIRIT (Standard Protocol Items: recommendations for Interventional Trials) statement[24]. The trial was registered at ClinicalTrials.gov prior to enrolment (NCT04673578). All

parents/guardians participating in the study will give electronically-documented informed consent; child and youth participants will provide informed assent or consent.

Study setting

This is a single-site study based at the British Columbia Children's Hospital (BCCH) Provincial OCD Program in Vancouver, BC, Canada. Study visits will be conducted virtually, utilizing electronic-consent and survey platforms through Research Electronic Data Capture (REDCap) and Zoom, an online videoconference platform that complies with the Personal Information Protection and Electronic Documents Act and the Personal Health Information Protection Act.

Patient selection

Participants will be recruited from BCCH and based on self-referral through community pediatrics, psychiatry, and psychology practices. Participants may be receiving concurrent pharmacotherapy or psychotherapy constituting "treatment-as-usual" as long as there have been no changes in the preceding 4 weeks and during the study period. They must have a previous diagnosis of OCD. Refer to Table 1 for full inclusion and exclusion criteria.

Allocation and randomization

Participants will be randomly assigned to either placebo or celecoxib with a 1:1 allocation as per a computer-generated randomization schedule stratified by baseline CY-BOCS score (16-23 versus ≥24) using permuted blocks of random sizes of 2 and 4. Specific information regarding the allocation sequence will be stored in a separate document with access restricted to the study's statistician, the Research Pharmacist, and a Research Assistant (RA) not involved in the study. The block sizes will not be disclosed to trial implementers.

Blinding

Trial participants, investigators, care providers, and outcome assessors will be blinded to treatment allocation. Placebo capsules will be identical in appearance to celecoxib capsules. Unique randomization codes will be used for each participant to avoid inadvertent loss of blinding for all participants in the event that one is unblinded. Data analysis and manuscript writing will be performed after unblinding once data have been cleaned for primary and secondary endpoints and AEs. Participants will be provided with an option to be contacted and informed of their allocation at that time. Emergency unblinding will occur only in exceptional circumstances when required to maintain participant safety – that is, when knowledge of the actual treatment is essential for further management. The blind will be maintained as far as possible and will not be disclosed to other study personnel unless required for patient management. Unblinding will not be a reason for study drug discontinuation.

Sample size calculation

The sample size of 80 participants (40 per arm) was estimated on the basis of the primary hypothesis. If we assume a power to detect a minimally clinically significant between-group difference in CY-BOCS scores of 2.5 with an SD of 5 (roughly based on the two existing studies of adjunctive celecoxib in adults[21,22]), a correlation of 0.5 between baseline and final CY-BOCS score, and a sample size of 40 participants per arm, we will have power of 80% to detect a between-group difference using a directional, one-tailed alpha (celecoxib<placebo) using analysis of covariance. Missing follow-up data due to attrition will be multiply imputed, allowing us to utilize the full sample size of 80 in this analysis. Our recruitment target is similar to pilot studies of adjunctive celecoxib in other psychiatric disorders[25].

Interventions

Eligible patients will be randomized to a 12-week course of either celecoxib (generic form) or placebo containing microcrystalline cellulose. Participants receiving celecoxib with weight between 10-25 kg, inclusive, will receive 50 mg twice daily; those >25 kg will receive 100 mg twice daily as per FDA-approved pediatric dosing in children. The placebo capsule is effectively indistinguishable from that of the drug. Participants will be instructed to take the capsule with food to reduce the risk of gastrointestinal side effects. Those unable to swallow a capsule may sprinkle the contents on moist food, given similar pharmacokinetics compared to an intact capsule[26]. Adherence will be documented by capsule count and adherence questionnaires. Weekly adherence reminders will be provided by email or text. Participants will also be asked to maintain an electronic diary documenting the first dose, missed doses, AEs, and changes to the usual way they take the capsule.

Participant schedule and follow-up

Prior to their first study visit, parents/guardians of participants who provide informed consent will complete a full eligibility screening questionnaire followed by a diagnostic interview that includes the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-Kid), a short structured interview that covers a broad range of DSM-5 psychiatric diagnoses in children and adolescents[27]. Participants and their parents who are eligible to proceed to the first study visit will complete a demographic/medical questionnaire and participant perspective questionnaire (PPQ) via REDCap prior to the first study visit.

Study visits will proceed according to the flow chart in Figure 1. Measures completed by a study physician at the first visit include the CY-BOCS[28]; Clinical Global Impression (CGI) scales [29]; review of diagnostic criteria for PANS/PANDAS, tic disorders, and restricted food intake[6], clinician treatment expectancy, and clinician experience of remote study visits. Participants who continue to meet eligibility criteria after Study Visit 1 will be provided with a requisition for monitoring blood work if not already completed (CBC, Cr, AST, ALT, electrolytes, pregnancy test). Participants will have the option to consent to participation in an ancillary study for biosample collection (blood, saliva, buccal swab, and stool) for future analyses of inflammatory markers.

For participants who remain eligible for randomization, the BCCH Pharmacy will dispense the study drug or placebo according to an allocation sequence provided to them by the team's statistician at a dose based on the patient's weight. For Visits 2 and 3, parents/participants will again complete a REDCap survey prior to each visit, including adherence and AE questionnaires. Participants will be provided with a requisition for blood work to be completed following Visit 3. Participants with ongoing symptoms (CY-BOCS>8) at Visit 3 will have the option to continue with a 12-week open-label extension with celecoxib, with a follow-up visit and monitoring blood work at 24 weeks.

OUTCOME PARAMETERS AND STATISTICAL ANALYSES

Primary Outcome

The primary outcome is OCD severity as measured by total CY-BOCS score after 12 weeks in the celecoxib compared to placebo arm, adjusted for baseline OCD severity. This is a more powerful statistical approach in comparison to analysis of change scores[30].

Secondary Outcomes

Secondary outcomes include the following: (1) OCD severity after 6 weeks of treatment in the celecoxib compared to placebo arm, adjusted for baseline OCD severity; (2) difference in the proportion of participants achieving a clinically meaningful response (defined as a 25% reduction in the CY-BOCS score or CGI-I of 1 or 2 based on previous meta-analyses[31]) after 6 and 12 weeks of treatment in the

celecoxib compared to placebo arm; (3) difference in the proportion of participants achieving clinical remission (CY-BOCS≤14) after 6 and 12 weeks of treatment in the celecoxib compared to placebo arm; (4) mean clinical global impression of severity (CGI-S) after 6 and 12 weeks in the celecoxib compared to placebo arm, adjusted for baseline OCD severity; (5) mean clinical global impression of improvement (CGI-I) after 6 and 12 weeks in the celecoxib compared to placebo arm, adjusted for baseline OCD severity; (6) difference between celecoxib and placebo arms in the proportion of participants reporting AEs that are possibly, probably, or definitely related to the study intervention.

Exploratory Outcomes

Exploratory analyses will include determination of the associations among age, sex, race/ethnicity, BMI percentile, treatment at baseline, severity at baseline, presence/severity of PANS/PANDAS symptoms or tics at any time point based on clinician assessment, medical/psychiatric comorbidities, time since diagnosis, scores on parent perspective questionnaire items, clinician treatment expectancy, and the primary and secondary outcomes. Additional measures of severity will be included in exploratory analyses and collected at all time points, including self-report and parent-report versions of the CY-BOCS and Obsessive Compulsive Inventory – Child Version (OCI-CV) (Table 2).

Outcome measures

Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS): OCD severity will be assessed using the CY-BOCS, a gold-standard clinician report measure[28]. The CY-BOCS is the most widely used measure of clinician-rated OCD and its psychometric properties including validity and reliability have been supported across many studies[32]. We have also included additional items in the clinician assessment forms to allow calculation of a score for CY-BOCS-II, which has been recently validated and may be used in future studies[33].

Clinical global impression (CGI): The CGI scale includes single item, clinician-rated, 7-point Likert-type scales of severity and improvement. The CGI-S is a frequently-used measure for assessment of symptom severity across multiple psychiatric illnesses. Both face-to-face and video scoring are considered valid outcome measures suitable for use in trials of OCD treatment[34]. The CGI-I typically but not always tracks with CGI-S[29] and has been used to define treatment response in treatment trials of pediatric OCD[31].

Participant perspective questionnaire (PPQ): This is a study-specific questionnaire to be completed online by the participant and parent in conjunction with each study visit. Included measures are listed in Table 2.

Clinician assessment: In addition to assessment of OCD severity, PANS/PANDAS diagnosis and review of tic symptoms/severity will be conducted by the clinician at all study visits. This will include CGI measures for tics and for food intake restriction (a PANS criterion). Clinicians will also complete several questions related to treatment expectancy and their experience of virtual study visits.

Adverse events: AEs will be systematically assessed at Study Visits 2 and 3 using a questionnaire adaptation of the Safety Monitoring Uniform Research Form (SMURF)[35]. The SMURF is an AE-elicitation tool specifically aimed at pediatric populations, developed by the NIMH-funded Research Units on Pediatric Psychopharmacology[35]. A checklist will also be included in participant electronic diaries to allow for standardization of reporting and to facilitate recall when completing the AE Questionnaire prior to the visit.

Adherence: Medication adherence questionnaires will be completed on REDCap by participants prior to Visits 2 and 3 and will be reviewed with the family by the RA and study physician. This will consist of

two questions regarding the frequency with which participants have taken all doses or missed one dose, with the response rated on a visual analogue scale. An open-ended question will be included regarding the reason for any missed doses. Adherence will also be assessed by capsule count at the end of the study.

Safety monitoring and interim analysis

This study will be reviewed by a Data Safety and Monitoring Board (DSMB). An interim analysis of recruitment rates and AEs will be conducted after the first 10 patients or the first year of recruitment. Unblinding of data will occur only at the request of the DSMB by a statistician not directly involved in the conduct of the study. No interim efficacy analysis is planned. Individual participants may be asked to leave the study for their own safety, in which case consensus of at least two study physicians will be required. Individual participants who withdraw from or complete the study will continue follow-up with their regular care providers.

Statistical analyses

Analyses will be carried out according to the intention-to-treat principle such that participants will be analyzed according to the group to which they were randomized regardless of adherence. Descriptive statistics will be conducted on baseline variables to evaluate the characteristics of the total sample and subsamples in each treatment condition. The primary analyses will be conducted on two sets of data. First, the analyses will be conducted on complete case data, which is defined as the set of subjects without missing data on the variables included in the particular statistical model. Second, missing data will be imputed using multivariate imputation by chained equations prior to being submitted to the statistical model. This approach is appropriate when data are missing at random or are missing completely at random[36]. The imputation method for all variables will be semi-parametric predictive mean matching, which restricts imputations to the observed values in the data set. Forty imputed data sets will be created following 40 iterations of a Gibbs sampler for each imputed data set. Proper convergence of the Gibbs sampler will be confirmed by visual inspection of trace plots of imputed variable, with an eye toward proper mixing and the absence of spikes or systematic trends across iterations. The imputation model will include all variables and interactions between variables that will ultimately be included in the primary, secondary and exploratory/subgroup analysis models. Thus, the imputation model will include baseline demographic and clinical characteristics used to form subgroups for exploratory analyses, treatment condition, baseline scores on outcomes measures, as well as observed follow-up scores on the outcomes of interest. Variables derived from other variables already included in the imputation model (e.g., CY-BOCS score ≤14 versus >14) will not be included in the imputation model. Statistical estimates will be pooled over the 40 imputed data sets using the Barnard-Rubin procedure to estimate pooled standard errors and degrees of freedom[37].

Primary Analysis: The primary analyses will compare the celecoxib to the placebo group on the outcome of interest at weeks 6 and 12, adjusting for baseline scores on the outcome, using ANCOVA for continuous outcomes and logistic regression for categorical outcomes. Additionally, baseline CY-BOCS will be included as a covariate in all analyses, even when CY-BOCS is not the outcome variable. ANCOVA produces unbiased treatment effect estimates and less variance in the treatment effect as compared to the commonly-used linear mixed model, resulting in superior statistical power[30]. All continuous outcomes believed to be generated from a Gaussian distribution will be analyzed using this approach.

The primary contrast for this study will be the between-group difference (celecoxib vs. placebo) in CY-BOCS score at 12 weeks, adjusted for baseline CY-BOCS score, using multiply-imputed data and complete case data. The estimated between-group difference using the multiply-imputed data will be considered the primary estimate; the estimated between-group difference using complete case data will be considered secondary. The statistical significance threshold for this analysis will be set at a one-sided

alpha = 0.05, to test whether the celecoxib group has lower adjusted 12-week CY-BOCS scores compared to the placebo group. For this analysis, we will report the between-group point estimate, 95% confidence value, and p-value to 3 decimal places. A p-value less than 0.001 will be reported as $p < 0.001$. Additional analyses of between-group differences in secondary outcomes and in symptom severity at the midpoint assessment will be considered descriptive and will be described using point estimates and 95% confidence intervals.

Secondary Analysis: Secondary analyses will include analysis of the proportion of patients in each group who achieve a 25% reduction in CY-BOCS score from baseline or CGI-I of 1 or 2 (treatment response) and who achieve a CY-BOCS score ≤14 (remission). Logistic regression will analyze between-group differences in this binary outcome (achieved ≥25% reduction versus did not), adjusting for baseline CY-BOCS score. Similarly, logistic regression will examine group differences in a binary AE variable (experienced at least one AE versus did not), also adjusting for baseline CY-BOCS score. Association between OCD symptoms, PGI, and treatment expectancy will be estimated using linear regression modelling with treatment group, age, sex, BMI percentile, race/ethnicity, PANS/PANDAS status, and tic status as covariates.

Other Analysis: Data collected during the 12-week extension period will be reported in a descriptive fashion, e.g., number of observations, percentages, means, and standard deviations.

Patient and public involvement

The research question addressed by the study has been informed by discussions with families interested in trialing NSAID therapy and the current lack of evidence base to inform treatment recommendations. Feedback from families has been incorporated into trial design, including addition of an open-label phase. Procedures for recruitment, assessment, BioBank sample collection, outcome assessments, follow-up, and results dissemination are common to other studies in the BCCH Provincial OCD Program that have provided both patients and families with an opportunity for input. Because this trial is unique in incorporating virtual/remote study visits for a pharmacological intervention within a pediatric psychiatric population in BC, participants' perspectives on their participation may provide critical information relevant to the design of future studies.

ETHICS AND DISSEMINATION

Data collection and confidentiality

All data are handled confidentially and the information in the datasets for analyses is non-identifiable.

Ethics

A No Objection Letter was received from Health Canada in January 2021 and the study was approved by the University of British Columbia / Children's and Women's Health Centre of British Columbia Research Ethics Board in April 2021. An amendment to include an open-label phase will be submitted in June 2021.

Withdrawal

Patients will be informed of their right to withdraw from the study without explanation at any time. In case of patient withdrawal, they will be asked for permission for prospective collection and later use of their hospital record data after their withdrawal.

Dissemination plan

The findings will be disseminated in peer-reviewed academic journals and presentations to multiple stakeholders including patients, parents, and health care providers.

DISCUSSION

This study will be the first to assess the efficacy of celecoxib in pediatric OCD. Multiple lines of evidence suggest behavioural effects of COX inhibition, which may relate not only to anti-inflammatory activity but also to direct effects on neuronal function and synaptic transmission. While clinical phenotyping will identify children meeting criteria for PANS/PANDAS, this work will also bring much-needed attention to a heterogeneous population of patients with OCD and may inform future trials of immune-modulating therapies. Participant perspectives on treatment expectancy, outcomes, and trial participation will be used to inform the design of future studies in this population.

***Rationale for use of a COX-2-selective versus COX-1-selective inhibitor*:** While all NSAIDS appear to have anti-inflammatory, antipyretic, and analgesic properties attributable to prostaglandin inhibition, they vary with respect to COX selectivity[38] and may have neuroprotective effects not directly related to their classic anti-inflammatory activity[39,40]. In the CNS, modulation of glutamate, serotonin, noepinephrine, and endocannabinoid signalling has been primarily demonstrated with COX-2 rather than COX-1 inhibitors[14,15,41-43]. Other than a negative RCT of naproxen in geriatric depression[44] and a study of adjuvant aspirin in schizophrenia[45], few RCTs have evaluated non-selective NSAIDs in primary psychiatric disorders. Given the significance of different COX isoforms and their unknown relative "potencies" in the CNS, careful attention must be given to selection and evaluation of specific NSAIDs to better understand their neurobiology and clinical efficacy. This study uses celecoxib rather than naproxen given evidence of benefit in adults with OCD and pre-clinical data pointing to modulation of serotonin and glutamate. Celecoxib is also associated with fewer gastrointestinal side effects in adults.

Rationale for dosing regimen: The US Food and Drug Administration has approved the use of celecoxib in the pediatric population for the management of juvenile idiopathic arthritis (JIA)[46] and is available in the US to children from ages two and up based on a non-inferiority study comparing celecoxib with naproxen[47]. A follow-up registry study from routine clinical practice included 274 children on NSAIDs and found that AEs were similar for non-selective NSAIDs and celecoxib, and that no serious AEs were attributed to NSAID use over a mean duration of treatment of 11-13 months[48]. The dosages used were within the range of those tested in children with JIA over 12 weeks (3-6 mg/kg twice daily)[47]. To avoid exceeding plasma levels associated with the 6 mg/kg suspension, the FDA-approved capsule dosing will be used in this study.

Strengths and limitations of this study: While an RCT of naproxen in PANDAS is currently recruiting (NCT04015596), the present study has broader inclusion criteria based on emerging evidence for inflammatory dysregulation in "classic" OCD and existing data in adults. The pragmatic approach of adding celecoxib to treatment-as-usual is a potential strength reflecting typical use in clinical practice. Because of this, our study population is likely to be more heterogeneous than that of existing adult studies. It is difficult to predict to what extent and in which direction selection bias will affect the representativeness of the study population, as in our clinical experience families often consider anti-inflammatory therapy at all stages and severities of the disorder.

A subset of children may benefit from immune-modulating therapies, but there are no validated strategies for identifying these individuals. This study incorporates biosample collection pre-and post-intervention, allowing not only for safety monitoring but also for future analyses of pro-inflammatory markers. Given the paucity of data from interventional trials examining longitudinal markers of inflammation and

treatment response in pediatric OCD, this will generate much-needed preliminary data to inform further studies of immune-related biomarkers. Due to funding limitations, these samples will be allocated for future analyses.

This study incorporates questionnaires aimed at better understanding participants' experiences virtual study visits, which is a novel format for psychopharmaceutical trials at our centre in the context of the COVID-19 pandemic and will increase equitable access to opportunities for research participation. We expect that these data will inform the design of future studies incorporating remote research visits and clinical care.

CONCLUSIONS

NSAIDs are common in clinical practice and referenced in both adult and pediatric treatment guidelines for OCD, but no controlled studies have evaluated the effects of COX inhibitors in childhood-onset OCD. This study will be the first to assess the efficacy and safety of adjunctive celecoxib in this population and will inform clinical management of children and youth with OCD.

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AUTHORS' CONTRIBUTIONS

CWR drafted the initial protocol under the supervision of SES, who revised for significant content. JB created the statistical analysis plan. MM, SB, DE, and LBT provided clinical input into study design and monitoring. AA, ZN, BL, and CL drafted subsections of the initial protocol and facilitated REB submission. All authors revised the protocol and approved of the final version to be submitted.

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COMPETING INTERESTS

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

TABLES

Table 1. Inclusion and exclusion criteria.

Criterion	Items
Inclusion	1. Age 7-18 years 2. Resident of British Columbia 3. DSM-5 diagnosis of OCD based on (a) history of prior clinician assessment and (b) standardized interview 4. Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) score ≥16 (moderate to severe) 5. Able to take medication twice daily in capsule form (in whole form or sprinkled contents) 6. Negative pregnancy test (either serum or urine) in participants with child-bearing potential 7. Use of highly effective and/or double barrier contraception, or abstinence, in participants with child-bearing potential
Exclusion	1. Lifetime diagnosis of autism spectrum disorder, bipolar disorder, psychotic disorder, substance-use disorder, intellectual disability, significant head injury causing loss of consciousness, renal disease, liver disease, gastrointestinal bleeding, peptic ulcer disease, inflammatory bowel disease, severe or uncontrolled asthma, bleeding disorders, heart disease, heart failure, or hypertension 2. Current major depressive episode, acute psychosis, active substance use, suicidality, or restriction of fluid intake 3. Pregnant or breastfeeding during the study period 4. Active infection or antibiotic treatment at baseline 5. Allergy to celecoxib, sulfonamide compounds, or NSAIDs, including aspirin 6. Current or previous regular use of immune-modulating therapies for treatment of OCD symptoms, at an effective anti-inflammatory dose (including NSAIDs, corticosteroids, or biologics) 7. Use of NSAIDs at any dose at a frequency ≥ 3 times per week during the 2 months prior to randomization 8. Current use of corticosteroids (IV, oral, inhaled, intranasal, or high-potency topical) 9. Concurrent use of CYP2C9 inhibitors fluconazole, amiodarone, oxandrolone or methotrexate; CYP2C9 inducers including rifampin and phenobarbital; or any other drug that may interact with celecoxib and, in the opinion of study physicians, represents a potential safety risk 10. Poor CYP2C9 metabolizer (i.e. CYP2C9*3/*3 genotype) based on clinical suspicion or previous genotyping 11. Abnormality identified on baseline serology including leukocytosis, leukopenia, thrombocytopenia, anemia, abnormal renal function (Cr > 1.5 x upper limit of normal), or abnormal liver function (ALT, ALP, or AST > 1.5x upper limit of normal) 12. New medication started in the 10 weeks prior to baseline, or change in dose in the 4 weeks prior to baseline 13. Changes in CBT or other psychotherapy in the 4 weeks prior to baseline (i.e. change in regular frequency, modality, or care provider) 14. Notable other treatment changes during the study period (either pharmacotherapy or psychotherapy) 15. No regular physician (family doctor or specialist) providing usual medical care 16. Participant/parents unable to provide informed consent or assent or participate in self-care, adverse event (AE) reporting, or follow-up assessments 17. Inability to have blood pressure measured within 2 months prior to enrollment (either on-site at BCCH or by a primary care provider) 18. Intention of pregnancy in participants with child-bearing potential

Table 2. Description of measures included in the parent/participant perspective questionnaire.

Measure	Outcome
Patient/Parent Global Impression scales for severity and improvement (PGI-S and PGI-I)	Severity and improvement in OCD and tic symptoms, based on a standard 7-point Likert scale derived from the Clinician Global Impression scales[49].
PANS Rating Scale	Severity and change in PANS/PANDAS symptoms[50]
National Institutes of Health PROMIS measures	Patient-reported measures of (a) global health, and (b) pain intensity, including 8 items overall[51,52].
Treatment expectancy	Two items assuming assignment of the participant to either placebo or active drug . Rated on a 7-point Likert scale, previously linked with treatment response and lower attrition in a clinical trial of CBT for youth with OCD[53].
Self-reported OCD severity	Self-report CY-BOCS, combining scores for obsessions and compulsions to generate a total score out of 20, consistent with recommendations based on a recent study of CY-BOCS construct validity[54].
Self-report and parent-report versions of the Obsessive Compulsive Inventory – Child Version (OCI-CV)	21-item self-report measure that assesses obsessive compulsive symptoms in children and adolescents aged 7 to 17 years over the preceding month[55].
Post-visit questionnaire items	Likert-scale and open-ended items querying participant experiences with virtual visits and trial participation using, based on previous work but tailored to this current study[56].

FIGURE 1

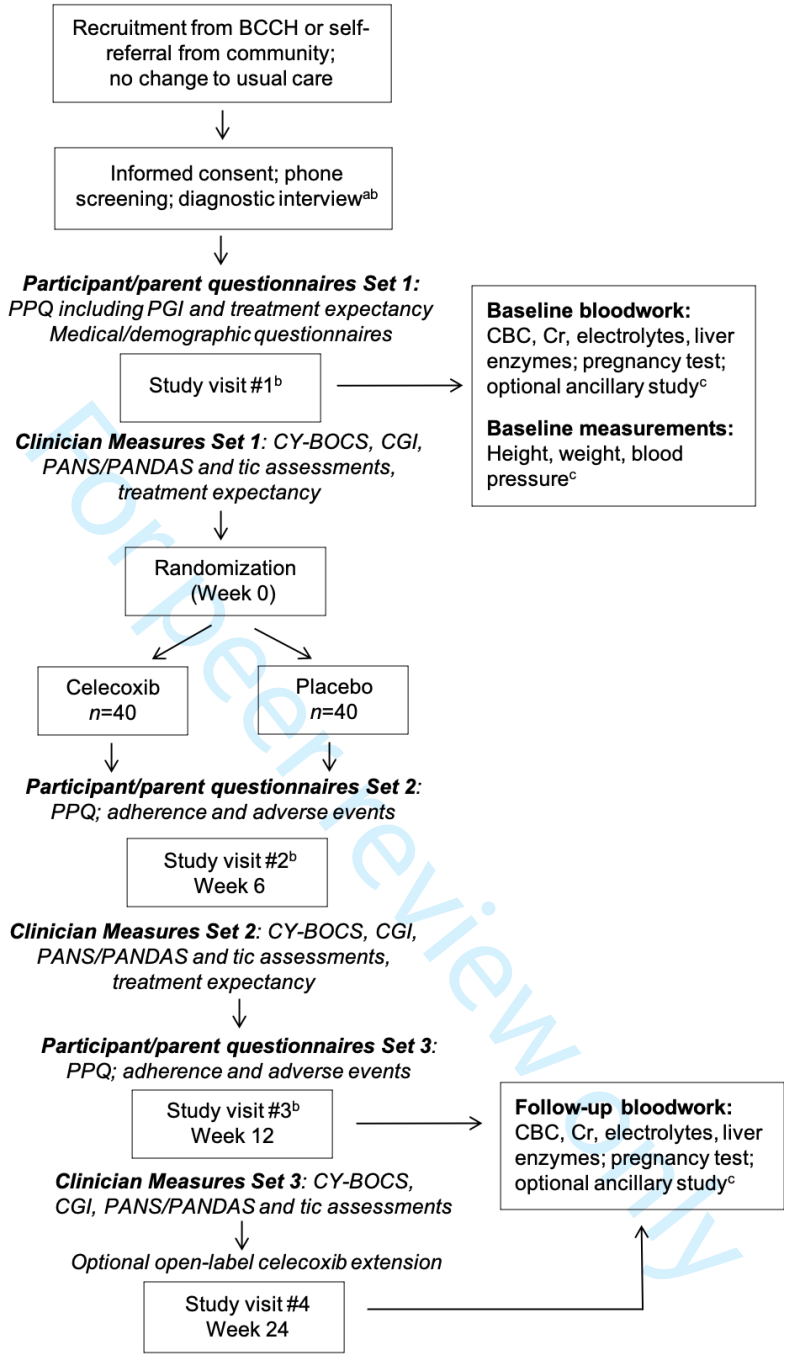

Figure 1. Flow diagram of study visits and assessments

[a] MINI-Kid diagnostic interview administered by phone with the participant and parent present.

[b]Screening and study visits may be conducted virtually according to patient preference and current COVID-19 restrictions.

[c]Height, weight, and blood pressure will be determined either on-site or by a participant's regular care provider.

[d]Participants will inform study staff of the date and time of their first dose. Weekly reminders regarding compliance and completion of the participant e-diary as required will be sent via email, phone, or text according to participant preference and consent.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Note that the main protocol for this study includes all items. This manuscript due to word count limitations includes only the following. For review purposes, refer to main SPIRIT checklist and protocol for further details.

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	NA (in main protocol)
Protocol version	#3	Date and version identifier	NA (in main protocol)
Funding	#4	Sources and types of financial, material, and other support	16
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	16
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	NA (in main protocol)
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for	16

		publication, including whether they will have ultimate authority over any of these activities	
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA (in main protocol)
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Table 1
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	NA (in main protocol)
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	NA (in main protocol)
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6-7
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6, Figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	5
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	5

		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA (in main protocol)
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	5
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	NA (in main protocol)
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	NA (in main protocol)
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8-9

Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8-9
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8-9
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	8
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	8
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA (in main protocol)
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	9
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	9
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	NA (in main protocol)

Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA (in main protocol)
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	NA (in main protocol)
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	NA (in main protocol)
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA (in main protocol)
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	9
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	NA (in main protocol)
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA (in main protocol)
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	NA (in main protocol)
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA (in main protocol)

Notes:

- 2b: NA (in main protocol)
- 3: NA (in main protocol)
- 5b: NA (in main protocol)
- 5d: NA (in main protocol)
- 11b: NA (in main protocol)
- 11c: NA (in main protocol)
- 13: 6, Figure 1
- 16c: NA (in main protocol)
- 18b: NA (in main protocol)
- 19: NA (in main protocol)
- 23: NA (in main protocol)
- 26a: NA (in main protocol)
- 26b: NA (in main protocol)
- 27: NA (in main protocol)
- 29: NA (in main protocol)
- 30: NA (in main protocol)
- 31b: NA (in main protocol)
- 31c: NA (in main protocol)
- 32: NA (in main protocol)
- 33: NA (in main protocol)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	9
Protocol version	3	Date and version identifier	5 (footer for all)
Funding	4	Sources and types of financial, material, and other support	1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	55
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	56
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	56-7

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	11-18
	6b	Explanation for choice of comparators	14
Objectives	7	Specific objectives or hypotheses	19
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	19
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	20
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	21
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	22
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	23
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	24
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	24
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*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Celecoxib versus placebo as an adjunct to treatment-as-usual in children and youth with obsessive-compulsive disorder: Protocol for a single-site randomized quadruple-blind phase II study

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Celecoxib versus placebo as an adjunct to treatment-as-usual in children and youth with obsessive-compulsive disorder: Protocol for a single-site randomized quadruple-blind phase II study

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Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ASD, autism spectrum disorder; BMI, body mass index, BCCH, British Columbia Children's Hospital; CGI, clinical global impression; CNS, central nervous system; C&W, Children's and Women's Health Centre; CBC, complete blood count; Cr, creatinine, COX, cyclooxygenase; CY-BOCS, Children's Yale-Brown Obsessive Compulsive Scale (Version I); CY-BOCS II, Children's Yale-Brown Obsessive Compulsive Scale (Version II); DSMB, data safety monitoring board; eCRF, electronic case report form; MDD, major depressive disorder; MINI-Kid, Mini International Neuropsychiatric Interview for Children and Adolescents; NSAID, Non-steroidal anti-inflammatory drug; OCD, obsessive-compulsive disorder; OCI-CV, Obsessive Compulsive Inventory – Child Version; PANS, pediatric acute neuropsychiatric syndrome; PANDAS, pediatric autoimmune disorder associated with streptococcal infections; PGI, patient global impression; PPQ, Participant Perspective Questionnaire; RCT, randomized controlled trial; RA, Research Assistant; REDCap, Research Electronic Data Capture; REB, Research Ethics Board; SMURF, Safety Monitoring Uniform Research Form; SRI, serotonin reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor

ABSTRACT

Background: Cyclooxygenase (COX) enzymes oxidize arachidonic acid to prostaglandins, which modulate neuronal function and inflammation in the central nervous system. Consensus guidelines suggest NSAIDs as a possible adjunctive approach in adults with obsessive-compulsive disorder (OCD) and in children with acute-onset OCD subtypes. However, there is limited evidence to support this approach. The primary objective of this study is to determine the efficacy of the COX-2-selective inhibitor celecoxib as an adjunct to treatment-as-usual in children and youth with moderate-to-severe OCD. The safety of this intervention including adverse events will also be systematically assessed.

Methods: The Adjunctive CElecoxib in childhood-onset OCD (ACE-OCD) study is a single-centre randomized, quadruple-blind, placebo-controlled superiority trial with two parallel groups: celecoxib 100 mg twice daily and placebo. Treatments will be added to participants' routine clinical care, which will not change over the course of the study. Target recruitment is 80 participants ages 7-18 with no recent treatment changes. The primary outcome is OCD severity after 12 weeks of treatment, measured by clinician-administered Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS). Secondary outcomes include CY-BOCS score after 6 weeks; difference in the proportion of participants achieving a clinically meaningful response or remission; mean clinical global impression of severity and improvement after 6 and 12 weeks; and proportion of participants reporting adverse events possibly or probably related to the study intervention. The primary analyses, carried out according to intention-to-treat principles, will compare the celecoxib to placebo group on each outcome of interest, adjusting for baseline scores using analysis of covariance or logistic regression. Participants will be offered a 12-week open-label celecoxib extension and will be invited to participate in an ancillary study for biomarker analyses.

Ethics and dissemination: This protocol has been approved by the University of British Columbia Children's and Women's Research Ethics Board and has received a No Objection Letter from Health Canada. The findings will be disseminated in peer-reviewed journals and presentations to multiple stakeholders including patients, parents, and health care providers.

Trial registration number: NCT04673578. Open for recruitment.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study is the first randomized, placebo-controlled trial to evaluate the efficacy and safety of adjunctive NSAID therapy in childhood-onset OCD and does not restrict participants to a diagnosis of pediatric acute-onset neuropsychiatric syndrome (PANS) or pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS).
- Study visits may occur virtually and screening blood work can be completed in participants' local communities, increasing accessibility for participants.
- Participants will have the option to consent to an ancillary study involving biosample collection for correlative biology; this will provide preliminary longitudinal data allowing measurement of associations between inflammatory biomarkers and clinical phenotype.
- This study incorporates assessment of participants' and parents' perspectives on participation, including their experience of virtual visits, to inform future studies of psychopharmacologic interventions in this population.
- While heterogeneity of usual therapy may limit power to detect differences between arms, this represents a more pragmatic approach than contemporaneous initiation of a selective serotonin reuptake inhibitor as described in preliminary studies in adults.

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a common neuropsychiatric condition identified by the World Health Organization as one of the leading causes of worldwide medical disability[1]. It affects 1-3% of the population and places significant burden on patients, families, and healthcare systems[2]. Childhood-onset OCD (CO-OCD) represents a specific subtype with unique epidemiological, etiological, and clinical characteristics[3,4]. Although cognitive behavioural therapy (CBT) and serotonin reuptake inhibitors (SRIs) are effective treatments, there is a critical need to develop novel and augmenting agents for patients with enduring symptoms.

A large body of work suggests an association between infection and an abrupt, early-onset form of OCD, termed pediatric autoimmune disorder associated with streptococcal infections (PANDAS)[5], as well as pediatric acute neuropsychiatric syndrome (PANS)[6]. Recent epidemiological data suggest that recurrent episodes of infection and inflammation are associated with the development of multiple mental disorders in children[7], including "classic" OCD[8]. Moreover, patients with autoimmune disorders have higher rates of comorbid OCD compared to the general population[9,10]. A recent cohort study based on Swedish National Register data suggested increased rates of multiple autoimmune diseases among patients with OCD and their first-degree relatives[11]; we have also described higher-than-expected rates of immune-related conditions in individuals with CO-OCD[12]. Positron emission tomography imaging study in adults with OCD has demonstrated increased volume of translocator protein-18 distribution in cortico-striato-thalamo-cortical circuits, implicating widespread microglial activation[13]. It is unclear whether changes in cellular and soluble inflammatory markers represent underlying etiology, a consequence of disease progression, or associated epiphenomena.

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase (COX) enzymes, which catalyze the metabolism of arachidonic acids to prostanoids. COX-2 and its products play an important physiological role in synaptic plasticity and long-term potentiation and may also contribute to neuropathology by enhancing glutamate excitotoxicity, promoting neuronal cell death, and oxidizing endogenous cannabinoids[14,15]. Recent meta-analyses suggest a potential role of adjunctive COX-2 inhibitors in the treatment of depression[16] and first-episode schizophrenia[17,18], with additional small studies suggesting possible benefit in neurodevelopmental conditions including autism spectrum disorder (ASD)[19,20]. Behavioral effects of COX inhibition may relate not only to anti-inflammatory activity but also to direct effects on neuronal function and synaptic transmission. Consensus guidelines on the use of anti-inflammatory therapy in children with PANDAS suggest NSAIDs as first-line options for patients with mild impairment[21]. However, a recent systematic review of treatment for PANS/PANDAS found insufficient evidence to support this practice[22]. In adults with OCD, three small randomized-controlled trials have suggested modest symptom improvement with celecoxib as an adjunct to fluoxetine[21], fluvoxamine[23,24], or other selective serotonin reuptake inhibitors (SSRIs)[25]. This raises the possibility that COX-2 inhibition may be effective in a general OCD population[26]. However, no controlled studies to date have tested the effects of COX inhibitors in CO-OCD. The present study will determine the efficacy of the COX-2-selective inhibitor celecoxib as an adjunct to treatment-as-usual in children and youth with moderate-to-severe OCD.

METHODS AND DESIGN

Study design

The ACE-OCD trial is a randomised, quadruple-blinded, placebo-controlled, single-site study comparing a 12-week course of twice daily celecoxib with placebo as an adjunct to treatment-as-usual in children and youth with moderate-to-severe OCD between the ages of 7 and 18. The protocol was drafted in

accordance with the SPIRIT (Standard Protocol Items: recommendations for Interventional Trials) statement[27]. The trial was registered at ClinicalTrials.gov prior to enrolment (NCT04673578). All parents/guardians participating in the study will give electronically-documented informed consent; child and youth participants will provide informed assent or consent.

Study setting

This is a single-site study based at the British Columbia Children's Hospital (BCCH) Provincial OCD Program in Vancouver, BC, Canada. Study visits will be conducted virtually, utilizing electronic-consent and survey platforms through Research Electronic Data Capture (REDCap) and Zoom, an online videoconference platform that complies with the Personal Information Protection and Electronic Documents Act and the Personal Health Information Protection Act. Participants will continue to receive treatment-as-usual from their regular health care providers, which will not change as a result of participation in this study.

Patient selection

Participants will be recruited from BCCH and based on self-referral through community pediatrics, psychiatry, and psychology practices. Participants may be receiving concurrent pharmacotherapy or psychotherapy according to their routine clinical care, constituting "treatment-as-usual" as long as there have been no changes in the preceding 4 weeks and during the study period. They must have a previous diagnosis of OCD. Participants with PANS or PANDAS who also meet diagnostic criteria for OCD are eligible to participate. Refer to Table 1 for full inclusion and exclusion criteria.

Allocation and randomization

Participants will be randomly assigned to either placebo or celecoxib with a 1:1 allocation as per a computer-generated randomization schedule stratified by baseline CY-BOCS score (16-23 versus ≥24) using permuted blocks of random sizes of 2 and 4. Specific information regarding the allocation sequence will be stored in a separate document with access restricted to the study's statistician, the Research Pharmacist, and a Research Assistant (RA) not involved in the study. The block sizes will not be disclosed to trial implementers.

Blinding

Trial participants, investigators, care providers, and outcome assessors will be blinded to treatment allocation. Placebo capsules will be identical in appearance to celecoxib capsules. Unique randomization codes will be used for each participant to avoid inadvertent loss of blinding for all participants in the event that one is unblinded. Data analysis and manuscript writing will be performed after unblinding once data have been cleaned for primary and secondary endpoints and AEs. Participants will be provided with an option to be contacted and informed of their allocation at that time. Emergency unblinding will occur only in exceptional circumstances when required to maintain participant safety – that is, when knowledge of the actual treatment is essential for further management. The blind will be maintained as far as possible and will not be disclosed to other study personnel unless required for patient management. Unblinding will not be a reason for study drug discontinuation.

Sample size calculation

The sample size of 80 participants (40 per arm) was estimated on the basis of the primary hypothesis. If we assume a power to detect a minimally clinically significant between-group difference in CY-BOCS scores of 2.5 with an SD of 5 (equivalent to a Cohen's d effect size of 0.5 and roughly based on two existing studies of adjunctive celecoxib in adults[23,24]), a correlation of 0.5 between baseline and final CY-BOCS score, and a sample size of 40 participants per arm, we will have power of 80% to detect a between-group difference using a directional, one-tailed alpha (celecoxib<placebo) using analysis of covariance.

Missing follow-up data due to attrition will be imputed (as described in detail in the Statistical Analysis section below). Our recruitment target is similar to pilot studies of adjunctive celecoxib in other psychiatric disorders[19].

Interventions

Eligible patients will be randomized to a 12-week course of either celecoxib (generic form) or placebo containing microcrystalline cellulose. Participants receiving celecoxib with weight between 10-25 kg, inclusive, will receive 50 mg twice daily (2-5 mg/kg per dose); those >25 kg will receive 100 mg twice daily as per FDA-approved pediatric dosing in children (maximum 4 mg/kg per dose). The placebo capsule is effectively indistinguishable from that of the drug. Participants will be instructed to take the capsule with food to reduce the risk of gastrointestinal side effects. Those unable to swallow a capsule may sprinkle the contents on moist food, given similar pharmacokinetics compared to an intact capsule[28]. Adherence will be documented by capsule count and adherence questionnaires. Weekly adherence reminders will be provided by email or text. Participants will also be asked to maintain an electronic diary documenting the first dose, missed doses, AEs, and changes to the usual way they take the capsule.

Participant schedule and follow-up

Prior to their first study visit, parents/guardians of participants who provide informed consent will complete a full eligibility screening questionnaire followed by a diagnostic interview that includes the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-Kid), a short structured interview that covers a broad range of DSM-5 psychiatric diagnoses in children and adolescents[29]. Participants and their parents who are eligible to proceed to the first study visit will complete a demographic/medical questionnaire and participant perspective questionnaire (PPQ) via REDCap prior to the first study visit.

Study visits will proceed according to the flow chart in Figure 1. Measures completed by a study physician at the first visit include the CY-BOCS[30]; Clinical Global Impression (CGI) scales [31]; review of diagnostic criteria for PANS/PANDAS, tic disorders, and restricted food intake[6], clinician treatment expectancy, and clinician experience of remote study visits. Participants who continue to meet eligibility criteria after Study Visit 1 will be provided with a requisition for monitoring blood work if not already completed (CBC, Cr, AST, ALT, electrolytes, pregnancy test). Participants will have the option to consent to participation in an ancillary study for biosample collection (blood, saliva, buccal swab, and stool) for future analyses of inflammatory markers.

For participants who remain eligible for randomization, the BCCH Pharmacy will dispense the study drug or placebo according to an allocation sequence provided to them by the team's statistician at a dose based on the patient's weight. For Visits 2 and 3, parents/participants will again complete a REDCap survey prior to each visit, including adherence and AE questionnaires. Participants will be provided with a requisition for blood work to be completed following Visit 3. Participants with ongoing symptoms (CY-BOCS>8) at Visit 3 will have the option to continue with a 12-week open-label extension with celecoxib, with a follow-up visit and monitoring blood work at 24 weeks. There is no cost to participate in the study.

OUTCOME PARAMETERS AND STATISTICAL ANALYSES

Primary Outcome

The primary outcome is OCD severity as measured by total CY-BOCS score after 12 weeks in the celecoxib compared to placebo arm, adjusted for baseline OCD severity. This is a more powerful statistical approach in comparison to analysis of change scores[32].

Secondary Outcomes

Secondary outcomes include the following: (1) OCD severity after 6 weeks of treatment in the celecoxib compared to placebo arm, adjusted for baseline OCD severity; (2) difference in the proportion of participants achieving a clinically meaningful response (defined as a 25% reduction in the CY-BOCS score or CGI-I of 1 or 2 based on previous meta-analyses[33]) after 6 and 12 weeks of treatment in the celecoxib compared to placebo arm; (3) difference in the proportion of participants achieving clinical remission (CY-BOCS≤14) after 6 and 12 weeks of treatment in the celecoxib compared to placebo arm; (4) mean clinical global impression of severity (CGI-S) after 6 and 12 weeks in the celecoxib compared to placebo arm, adjusted for baseline OCD severity; (5) mean clinical global impression of improvement (CGI-I) after 6 and 12 weeks in the celecoxib compared to placebo arm, adjusted for baseline OCD severity; (6) difference between celecoxib and placebo arms in the proportion of participants reporting AEs that are possibly, probably, or definitely related to the study intervention. Definitions of response and remission are applied as described previously to allow for cross-study comparability[34].

Exploratory Outcomes

Exploratory analyses will include determination of the associations among age, sex, race/ethnicity, BMI percentile, treatment at baseline, severity at baseline, presence/severity of PANS/PANDAS symptoms or tics at any time point based on clinician assessment, medical/psychiatric comorbidities, time since diagnosis, scores on parent perspective questionnaire items, clinician treatment expectancy, and the primary and secondary outcomes. Additional measures of severity will be included in exploratory analyses and collected at all time points, including self-report and parent-report versions of the CY-BOCS and Obsessive Compulsive Inventory – Child Version (OCI-CV) (Table 2).

Outcome measures

Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS): OCD severity will be assessed using the CY-BOCS, a gold-standard clinician report measure[30]. The CY-BOCS is the most widely used measure of clinician-rated OCD and its psychometric properties including validity and reliability have been supported across many studies[35]. It is comprised of two subscale total scores, Obsessions and Compulsions, each ranging from 0-20, with a higher score indicating greater symptom severity. These subscale scores are summed to provide a total score, ranging from 0 to 40, that is used to measure overall OCD symptom severity. We have also included additional items in the clinician assessment forms to allow calculation of a score for CY-BOCS-II, which has been recently validated and may be used in future studies[36].

Clinical global impression (CGI): The CGI scale includes single item, clinician-rated, 7-point Likert-type scales of severity and improvement. The CGI-S is a frequently-used measure for assessment of symptom severity across multiple psychiatric illnesses. Both face-to-face and video scoring are considered valid outcome measures suitable for use in trials of OCD treatment[37]. The CGI-I typically but not always tracks with CGI-S[31] and has been used to define treatment response in treatment trials of pediatric OCD[33].

Participant perspective questionnaire (PPQ): This is a study-specific questionnaire to be completed online by the participant and parent in conjunction with each study visit. Included measures are listed in Table 2.

PANDAS/PANS scale: Included in the PPQ, this rating scale assesses severity and change in PANS/PANDAS symptoms and is a parent self-report form based on criteria proposed by the PANS Consortium and described previously[38]. This measure has also been used to capture PANS exacerbation, as it asks the rater whether each current symptom had been possibly worse (1 point), dramatically worse

(2 points), new (3 points), or better/same (0 points) within the past week. The maximum score possible is 54[38].

Clinician assessment: In addition to assessment of OCD severity, PANS/PANDAS diagnosis and review of tic symptoms/severity will be conducted by the clinician at all study visits. This will include CGI measures for tics and for food intake restriction (a PANS criterion). Clinicians will also complete several questions related to treatment expectancy and their experience of virtual study visits.

Adverse events: AEs will be systematically assessed at Study Visits 2 and 3 using a questionnaire adaptation of the Safety Monitoring Uniform Research Form (SMURF)[39]. The SMURF is an AE-elicitation tool specifically aimed at pediatric populations, developed by the NIMH-funded Research Units on Pediatric Psychopharmacology[39]. A checklist will also be included in participant electronic diaries to allow for standardization of reporting and to facilitate recall when completing the AE Questionnaire prior to the visit.

Adherence: Medication adherence questionnaires will be completed on REDCap by participants prior to Visits 2 and 3 and will be reviewed with the family by the RA and study physician. This will consist of two questions regarding the frequency with which participants have taken all doses or missed one dose, with the response rated on a visual analogue scale. An open-ended question will be included regarding the reason for any missed doses. Adherence will also be assessed by capsule count at the end of the study.

Safety monitoring and interim analysis

This study will be reviewed by a Data Safety and Monitoring Board (DSMB). An interim analysis of recruitment rates and AEs will be conducted after the first 10 patients or the first year of recruitment. Unblinding of data will occur only at the request of the DSMB by a statistician not directly involved in the conduct of the study. No interim efficacy analysis is planned. Individual participants may be asked to leave the study for their own safety, in which case consensus of at least two study physicians will be required. Individual participants who withdraw from or complete the study will continue follow-up with their regular care providers.

Statistical analyses

Analyses will be carried out according to the intention-to-treat principle such that participants will be analyzed according to the group to which they were randomized regardless of adherence. Descriptive statistics will be conducted on baseline variables to evaluate the characteristics of the total sample and subsamples in each treatment condition. The primary analyses will be conducted on two sets of data. First, the analyses will be conducted on complete case data, which is defined as the set of subjects without missing data on the variables included in the particular statistical model. Second, missing data will be multiply imputed using the multivariate imputation by chained equations approach, which is appropriate when data are missing at random or are missing completely at random[40]. The imputation method for all variables will be semi-parametric predictive mean matching, which restricts imputations to the observed values in the data set. Common diagnostics, including visual inspection of trace plots and examination of R-hat values, will be used to ensure the validity of the imputation procedure. The imputation model will include baseline demographic and clinical characteristics used to form subgroups for exploratory analyses, treatment condition, baseline scores on outcomes measures, as well as observed follow-up scores on the outcomes of interest. The imputation model will create forty imputed data sets, on which statistical analyses will be performed. Statistical estimates will be pooled over the 40 imputed data sets using the Barnard-Rubin procedure to estimate pooled standard errors and degrees of freedom[41].

Primary Analysis: The primary analyses will compare the celecoxib to the placebo group on the outcome of interest at weeks 6 and 12, adjusting for baseline scores on the outcome, using ANCOVA for continuous outcomes and logistic regression for categorical outcomes. Additionally, baseline CY-BOCS will be included as a covariate in all analyses, even when CY-BOCS is not the outcome variable. ANCOVA produces unbiased treatment effect estimates and less variance in the treatment effect as compared to the commonly-used linear mixed model, resulting in superior statistical power[32]. All continuous outcomes believed to be generated from a Gaussian distribution will be analyzed using this approach.

The primary contrast for this study will be the between-group difference (celecoxib vs. placebo) in CY-BOCS score at 12 weeks, adjusted for baseline CY-BOCS score, using multiply-imputed data and complete case data. The estimated between-group difference using the multiply-imputed data will be considered the primary estimate; the estimated between-group difference using complete case data will be considered secondary. The statistical significance threshold for this analysis will be set at a one-sided alpha = 0.05, to test whether the celecoxib group has lower adjusted 12-week CY-BOCS scores compared to the placebo group. For this analysis, we will report the between-group point estimate, 95% confidence value, and p-value to 3 decimal places. A *p*-value less than 0.001 will be reported as $p < 0.001$. Additional analyses of between-group differences in secondary outcomes and in symptom severity at the midpoint assessment will be considered descriptive and will be described using point estimates and 95% confidence intervals.

Secondary Analysis: Secondary analyses will include analysis of the proportion of patients in each group who achieve a 25% reduction in CY-BOCS score from baseline or CGI-I of 1 or 2 (treatment response) and who achieve a CY-BOCS score ≤14 (remission). Logistic regression will analyze between-group differences in this binary outcome (achieved ≥25% reduction versus did not), adjusting for baseline CY-BOCS score. Similarly, logistic regression will examine group differences in a binary AE variable (experienced at least one AE versus did not), also adjusting for baseline CY-BOCS score. Association between OCD symptoms, PGI, and treatment expectancy will be estimated using linear regression modelling with treatment group, age, sex, BMI percentile, race/ethnicity, PANS/PANDAS status, and tic status as covariates.

Other Analysis: Data collected during the 12-week extension period will be reported in a descriptive fashion, e.g., number of observations, percentages, means, and standard deviations.

Patient and public involvement

The research question addressed by the study has been informed by discussions with families interested in trialing NSAID therapy and the current lack of evidence base to inform treatment recommendations. Feedback from families has been incorporated into trial design, including addition of an open-label phase. Procedures for recruitment, assessment, BioBank sample collection, outcome assessments, follow-up, and results dissemination are common to other studies in the BCCH Provincial OCD Program that have provided both patients and families with an opportunity for input. Because this trial is unique in incorporating virtual/remote study visits for a pharmacological intervention within a pediatric psychiatric population in BC, participants' perspectives on their participation may provide critical information relevant to the design of future studies.

ETHICS AND DISSEMINATION

Data collection and confidentiality

All data are handled confidentially and the information in the datasets for analyses is non-identifiable.

Ethics

A No Objection Letter has been received from Health Canada. This study has been approved by the University of British Columbia / Children's and Women's Health Centre of British Columbia Research Ethics Board.

Withdrawal

Patients will be informed of their right to withdraw from the study without explanation at any time. In case of patient withdrawal, they will be asked for permission for prospective collection and later use of their hospital record data after their withdrawal.

Dissemination plan

The findings will be disseminated in peer-reviewed academic journals and presentations to multiple stakeholders including patients, parents, and health care providers.

DISCUSSION

This study will be the first to assess the efficacy of celecoxib in pediatric OCD. Multiple lines of evidence suggest behavioural effects of COX inhibition, which may relate not only to anti-inflammatory activity but also to direct effects on neuronal function and synaptic transmission. While clinical phenotyping will identify children meeting criteria for PANS/PANDAS, this work will also bring much-needed attention to a heterogeneous population of patients with OCD and may inform future trials of immune-modulating therapies. Participant perspectives on treatment expectancy, outcomes, and trial participation will be used to inform the design of future studies in this population.

***Rationale for use of a COX-2-selective versus COX-1-selective inhibitor*:** While all NSAIDS appear to have anti-inflammatory, antipyretic, and analgesic properties attributable to prostaglandin inhibition, they vary with respect to COX selectivity[42] and may have neuroprotective effects not directly related to their classic anti-inflammatory activity[43,44]. In the CNS, modulation of glutamate, serotonin, norepinephrine, and endocannabinoid signalling has been primarily demonstrated with COX-2 rather than COX-1 inhibitors[14,15,45-47]. Other than a negative RCT of naproxen in geriatric depression[48] and a study of adjuvant aspirin in schizophrenia[49], few RCTs have evaluated non-selective NSAIDs in primary psychiatric disorders. Given the significance of different COX isoforms and their unknown relative "potencies" in the CNS, careful attention must be given to selection and evaluation of specific NSAIDs to better understand their neurobiology and clinical efficacy. This study uses celecoxib rather than naproxen given evidence of benefit in adults with OCD and pre-clinical data pointing to modulation of serotonin and glutamate. Celecoxib is also associated with fewer gastrointestinal side effects in adults.

Rationale for dosing regimen: The US Food and Drug Administration has approved the use of celecoxib in the pediatric population for the management of juvenile idiopathic arthritis (JIA)[50] and is available in the US to children from ages two and up based on a non-inferiority study comparing celecoxib with naproxen[51]. A follow-up registry study from routine clinical practice included 274 children on NSAIDs and found that AEs were similar for non-selective NSAIDs and celecoxib, and that no serious AEs were attributed to NSAID use over a mean duration of treatment of 11-13 months[52]. The dosages used were within the range of those tested in children with JIA over 12 weeks (3-6 mg/kg twice daily)[51]. To avoid exceeding plasma levels associated with the 6 mg/kg suspension, the FDA-approved capsule dosing will be used in this study.

Strengths and limitations of this study: While an RCT of naproxen in PANDAS is currently recruiting

(NCT04015596), the present study has broader inclusion criteria based on emerging evidence for inflammatory dysregulation in "classic" OCD and existing data in adults. The pragmatic approach of adding celecoxib to treatment-as-usual is a potential strength reflecting typical use in clinical practice. Because of this, our study population is likely to be more heterogeneous than that of existing adult studies. It is difficult to predict to what extent and in which direction selection bias will affect the representativeness of the study population, as in our clinical experience families often consider anti-inflammatory therapy at all stages and severities of the disorder.

A subset of children may benefit from immune-modulating therapies, but there are no validated strategies for identifying these individuals. This study incorporates biosample collection pre-and post-intervention, allowing not only for safety monitoring but also for future analyses of pro-inflammatory markers. Given the paucity of data from interventional trials examining longitudinal markers of inflammation and treatment response in pediatric OCD, this will generate much-needed preliminary data to inform further studies of immune-related biomarkers. Due to funding limitations, these samples will be allocated for future analyses.

This study incorporates questionnaires aimed at better understanding participants' experiences virtual study visits, which is a novel format for psychopharmaceutical trials at our centre in the context of the COVID-19 pandemic and will increase equitable access to opportunities for research participation. We expect that these data will inform the design of future studies incorporating remote research visits and clinical care.

CONCLUSIONS

NSAIDs are common in clinical practice and referenced in both adult and pediatric treatment guidelines for OCD, but no controlled studies have evaluated the effects of COX inhibitors in childhood-onset OCD. This study will be the first to assess the efficacy and safety of adjunctive celecoxib in this population and will inform clinical management of children and youth with OCD.

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FIGURE LEGENDS

Figure 1. Flow diagram of study visits and assessments.
[a]MINI-Kid diagnostic interview administered by phone with the participant and parent present.
[b]Screening and study visits may be conducted virtually according to patient preference and current COVID-19 restrictions.
[c]Height, weight, and blood pressure will be determined either on-site or by a participant's regular care provider.
[d]Participants will inform study staff of the date and time of their first dose. Weekly reminders regarding compliance and completion of the participant e-diary as required will be sent via email, phone, or text according to participant preference and consent.

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AUTHORS' CONTRIBUTIONS
CWR drafted the initial protocol under the supervision of SES, who revised for significant content. JB created the statistical analysis plan. MM, SB, DE, and LBT provided clinical input into study design and monitoring. AA, ZN, BL, and CL drafted subsections of the initial protocol and facilitated research ethics board submission. All authors revised the protocol and approved of the final version to be submitted.

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COMPETING INTERESTS
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

TABLES

Table 1. Inclusion and exclusion criteria.

Criterion	Items
Inclusion	1. Age 7-18 years 2. Resident of British Columbia, Canada 3. DSM-5 diagnosis of OCD based on (a) history of prior clinician assessment and (b) standardized interview 4. Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) score ≥16 (moderate to severe) 5. Able to take medication twice daily in capsule form (in whole form or sprinkled contents) 6. Negative pregnancy test (either serum or urine) in participants with child-bearing potential 7. Use of highly effective and/or double barrier contraception, or abstinence, in participants with child-bearing potential
Exclusion	1. Lifetime diagnosis of autism spectrum disorder, bipolar disorder, psychotic disorder, substance-use disorder, intellectual disability, significant head injury causing loss of consciousness, renal disease, liver disease, gastrointestinal bleeding, peptic ulcer disease, inflammatory bowel disease, severe or uncontrolled asthma, bleeding disorders, heart disease, heart failure, or hypertension 2. Current major depressive episode, acute psychosis, active substance use, suicidality, or restriction of fluid intake 3. Pregnant or breastfeeding during the study period 4. Active infection or antibiotic treatment at baseline 5. Allergy to celecoxib, sulfonamide compounds, or NSAIDs, including aspirin 6. Current or previous regular use of immune-modulating therapies for treatment of OCD symptoms, at an effective anti-inflammatory dose (including NSAIDs, corticosteroids, or biologics) 7. Use of NSAIDs at any dose at a frequency ≥ 3 times per week during the 2 months prior to randomization 8. Current use of IV or oral corticosteroids 9. Concurrent use of CYP2C9 inhibitors fluconazole, amiodarone, oxandrolone or methotrexate; CYP2C9 inducers including rifampin and phenobarbital; or any other drug that may interact with celecoxib and, in the opinion of study physicians, represents a potential safety risk 10. Poor CYP2C9 metabolizer (i.e. CYP2C9*3/*3 genotype) based on clinical suspicion or previous genotyping 11. Abnormality identified on baseline serology including leukocytosis, leukopenia, thrombocytopenia, anemia, abnormal renal function (Cr > 1.5 x upper limit of normal), or abnormal liver function (ALT, ALP, or AST > 1.5x upper limit of normal) 12. New medication started in the 4 weeks prior to baseline, or change in dose in the 2 weeks prior to baseline 13. Changes in CBT or other psychotherapy in the 2 weeks prior to baseline (i.e. change in regular frequency, modality, or care provider) 14. Notable other treatment changes during the study period (either pharmacotherapy or psychotherapy) 15. No regular physician (family doctor or specialist) providing usual medical care 16. Participant/parents unable to provide informed consent or assent or participate in self-care, adverse event (AE) reporting, or follow-up assessments 17. Inability to have blood pressure measured within 2 months prior to enrollment (either on-site at BCCH or by a primary care provider) 18. Intention of pregnancy in participants with child-bearing potential

Table 2. Description of measures included in the parent/participant perspective questionnaire.

Measure	Outcome
Patient/Parent Global Impression scales for severity and improvement (PGI-S and PGI-I)	Severity and improvement in OCD and tic symptoms, based on a standard 7-point Likert scale derived from the Clinician Global Impression scales[53].
PANS Rating Scale	Severity and change in PANS/PANDAS symptoms[38]
National Institutes of Health PROMIS measures	Patient-reported measures of (a) global health, and (b) pain intensity, including 8 items overall[54,55].
Treatment expectancy	Two items assuming assignment of the participant to either placebo or active drug . Rated on a 7-point Likert scale, previously linked with treatment response and lower attrition in a clinical trial of CBT for youth with OCD[56].
Self-reported OCD severity	Self-report CY-BOCS, combining scores for obsessions and compulsions to generate a total score out of 20, consistent with recommendations based on a recent study of CY-BOCS construct validity[57].
Self-report and parent-report versions of the Obsessive Compulsive Inventory – Child Version (OCI-CV)	21-item self-report measure that assesses obsessive compulsive symptoms in children and adolescents aged 7 to 17 years over the preceding month[58].
Post-visit questionnaire items	Likert-scale and open-ended items querying participant experiences with virtual visits and trial participation using, based on previous work but tailored to this current study[59].

FIGURE 1

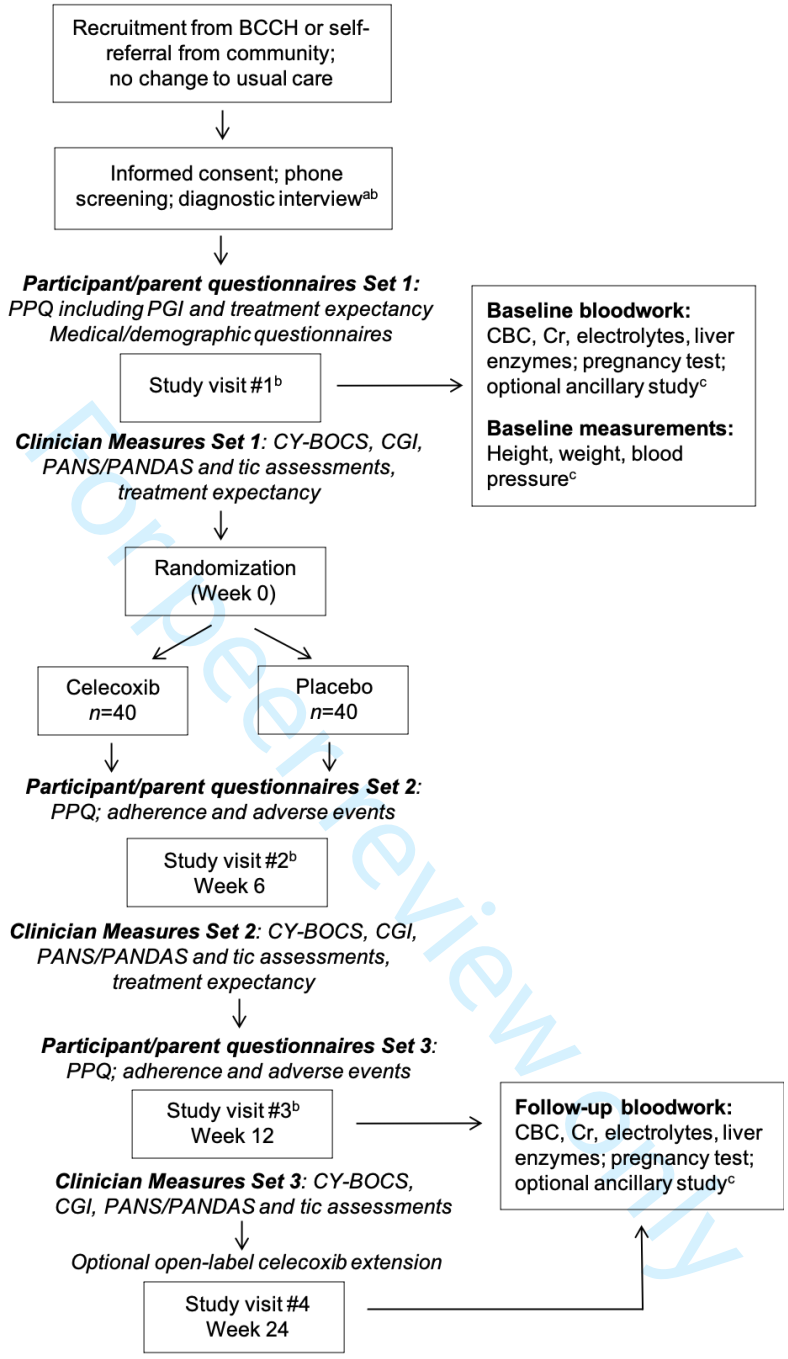

Figure 1. Flow diagram of study visits and assessments

[a] MINI-Kid diagnostic interview administered by phone with the participant and parent present.

[b]Screening and study visits may be conducted virtually according to patient preference and current COVID-19 restrictions.

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Note that the main protocol for this study includes all items. This manuscript due to word count limitations includes only the following. For review purposes, refer to main SPIRIT checklist and protocol for further details.

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	NA (in main protocol)
Protocol version	#3	Date and version identifier	NA (in main protocol)
Funding	#4	Sources and types of financial, material, and other support	16
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	16
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	NA (in main protocol)
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for	16

		publication, including whether they will have ultimate authority over any of these activities	
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA (in main protocol)
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Table 1
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	NA (in main protocol)
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	NA (in main protocol)
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6-7
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6, Figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	5
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	5

		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA (in main protocol)
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	5
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	NA (in main protocol)
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	NA (in main protocol)
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8-9

Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8-9
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8-9
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	8
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	8
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA (in main protocol)
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	9
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	9
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	NA (in main protocol)

Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA (in main protocol)
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	NA (in main protocol)
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	NA (in main protocol)
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA (in main protocol)
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	9
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	NA (in main protocol)
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA (in main protocol)
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	NA (in main protocol)
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA (in main protocol)

Notes:

- 2b: NA (in main protocol)
- 3: NA (in main protocol)
- 5b: NA (in main protocol)
- 5d: NA (in main protocol)
- 11b: NA (in main protocol)
- 11c: NA (in main protocol)
- 13: 6, Figure 1
- 16c: NA (in main protocol)
- 18b: NA (in main protocol)
- 19: NA (in main protocol)
- 23: NA (in main protocol)
- 26a: NA (in main protocol)
- 26b: NA (in main protocol)
- 27: NA (in main protocol)
- 29: NA (in main protocol)
- 30: NA (in main protocol)
- 31b: NA (in main protocol)
- 31c: NA (in main protocol)
- 32: NA (in main protocol)
- 33: NA (in main protocol)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	9
Protocol version	3	Date and version identifier	5 (footer for all)
Funding	4	Sources and types of financial, material, and other support	1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	55
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	56
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	56-7

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	11-18
	6b	Explanation for choice of comparators	14
Objectives	7	Specific objectives or hypotheses	19
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	19
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	20
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	21
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	22
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	23
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	24
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	24
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	25
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	26

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	31
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	31
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	32
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	33
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	33
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	33
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	34
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	34
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	37

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	38
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	40
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	41
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	40
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	43
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	43
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	44
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	47
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	48
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	48

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	49
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	50
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	51
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	51
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	52
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	52
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	53
	31b	Authorship eligibility guidelines and any intended use of professional writers	53
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	53
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	57
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	58

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.